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Fulminant *Clostridium difficile*: An Underappreciated and Increasing Cause of Death and Complications

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Objective
To review the epidemiology and characteristics of patients who died or underwent colectomy secondary to fulminant *Clostridium difficile* colitis.

Summary Background Data
In patients with *C. difficile* colitis, a progressive, systemic inflammatory state may develop that is unresponsive to medical therapy; it may progress to colectomy or death.

Methods
The authors reviewed 2,334 hospitalized patients with *C. difficile* colitis from January 1989 to December 2000. Sixty-four patients died or underwent colectomy for pathologically proven *C. difficile* colitis.

Results
In 2000, the incidence of *C. difficile* colitis in hospitalized patients increased from a baseline of 0.68% to 1.2%, and the incidence of patients with *C. difficile* colitis in whom life-threatening symptoms developed increased from 1.6% to 3.2%. Forty-four patients required a colectomy and 20 others died directly from *C. difficile* colitis. Twenty-two percent had a prior history of *C. difficile* colitis. A recent surgical procedure and immunosuppression were common predisposing conditions. Lung transplant patients were 46 times more likely to have *C. difficile* colitis and eight times more likely to have severe disease. Abdominal computed tomography scan correctly diagnosed all patients, whereas 12.5% of toxin assays and 10% of endoscopies were falsely negative. Patients undergoing colectomy for *C. difficile* colitis had an overall death rate of 57%. Significant predictors of death after colectomy were preoperative vasopressor requirements and age.

Conclusions
C. difficile colitis is a significant and increasing cause of death. Surgical treatment of *C. difficile* colitis has a high death rate once the fulminant expression of the disease is present.

Clostridium difficile is a spore-forming gram-positive bacteria first identified as the cause of antibiotic-associated diarrhea and colitis in the late 1970s.[1,2] The clinical symptoms range from mild diarrhea to hemodynamic collapse and death. Recent antimicrobial use (<2 months) is the most important risk factor for the development of *C. difficile* colitis; however, host and environmental factors also play a significant role.[3,4] Most cases can be treated by the administration of metronidazole or vancomycin to reverse the overgrowth of *C. difficile* and its toxin production in the colon, but a wide spectrum of disease exists; in some patients life-threatening systemic toxicity develops despite appropriate and timely medical therapy.[5,6] A classification scheme of disease severity is detailed in Table 1. Systemic symptoms are not derived from bacteremia, colonic perforation, or ischemia, but from toxin-induced inflammatory mediators (interleukin-8, macrophage-inflammatory protein-2, substance P, tumor necrosis factor-α) released locally in the colon.[7–9] Why some patients have more marked symptoms than others is unclear but may relate to the host's ability to mount an effective antibody-mediated response to clostridial toxins.[10,11] Uncharacterized geographic factors

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Table 1. SEVERITY CLASSIFICATION SCHEME IN PATIENTS WITH *CLOSTRIDIUM DIFFICILE*

	Heart Rate	Percent Band Forms	Respiratory Status	Oliguria	Hypotension
Mild disease	Normal	Normal	Normal	None	Not present
Moderate disease	>90	>10% bands	Mild tachypnea	Responds to volume	>100 systolic
Fulminant disease	>120	>30% bands	Requiring mechanical intubation	Severe	Requires vasopressors

also seem to play a major role in the incidence and severity of disease.

Total abdominal colectomy and end ileostomy, the standard surgical treatment for patients with severe *C. difficile* colitis, has been described only in small series, the largest (n = 12) from our hospital published in 1992.[12–16] Recently we have noted an increase in the number of emergency colectomies for this disease. The purpose of the study was to define the epidemiology, clinical presentation, and risk factors peculiar to the fulminant syndrome. In addition, we tried to determine predictors of surgical death.

METHODS

All patients who had a diagnostic code for *C. difficile* colitis at hospital discharge and all patients who otherwise had a positive cytotoxin assay for the 12-year period from January 1989 to December 2000 were identified. Overall hospital admissions and death rates were obtained to calculate the incidence of *C. difficile* colitis at UPMC-Presbyterian Hospital, a tertiary university hospital that admits approximately 29,000 patients a year. A more detailed computer-directed chart review through the University of Pittsburgh Medical Archive and Retrieval System (MARS) was used to identify all patients in the 12-year period from January 1989 through December 2000 who had undergone colectomy or were found to have *C. difficile* colitis at autopsy.

We use the term "fulminant colitis" in any patient with a systemic inflammatory syndrome (fever, hypotension, tachypnea, leukocytosis, and/or a requirement for volume resuscitation) that resulted in death or an illness severe enough that that death seemed likely without urgent colectomy (see Table 1). Further, to ensure there was no confusion in the primary cause of death, this study included only those patients whose diagnosis was confirmed through gross and microscopic pathology. No children were included. Forty-four adult patients underwent a colectomy for *C. difficile* colitis. Another 20 adult patients who did not undergo colectomy were identified by autopsy records to have their primary cause of death as *C. difficile* colitis. Four patients of this autopsied group underwent a "nontherapeutic" exploratory laparotomy but had *C. difficile* colitis listed as the primary cause of death. These patients were included in the nontreatment, autopsy group. In calculating the incidence of fulminant *C. difficile* colitis from our inpatient population, we excluded patients who were transferred with the diagnosis of fulminant *C. difficile* colitis because they would have falsely elevated our nosocomial incidence.

Twenty patients (45%) who underwent colectomy had longitudinal APACHE III data obtained from a prospective database that became available on intensive care unit patients after 1996. APACHE III data were recorded for a period of up to 3 days before colectomy. Pre-event laboratory data obtained within 48 hours of colectomy or death were examined, including peripheral blood leukocyte count and differential, blood gases, and lactate.

No strict protocol for the timing of surgical intervention had been followed through the study period; however, our general practice has been to recommend colectomy in patients with *C. difficile* colitis requiring vasopressors despite adequate volume resuscitation.[12] Patients exhibiting peritoneal signs or those who are obviously failing to respond to medical therapy with life-threatening systemic symptoms despite appropriate antibiotic usage are also surgical candidates. Immunosuppression was defined as any patient receiving medications such as corticosteroids, chemotherapy, tacrolimus, or cyclosporin. Also, patient with hematologic malignancies, HIV, and autoimmune disorders requiring steroids were categorized as immunosuppressed.

A Student *t* test and Mann-Whitney rank sum test were used to determine significance between groups of patients. All statistical variation is reported as standard deviations.

RESULTS

Epidemiology

Table 2 shows the demographic data. During the 12-year period from January 1989 to December 2000, there were 345,600 admissions to UPMC-Presbyterian Hospital. The incidence of *C. difficile* colitis as a function of all hospital admissions was stable through the period 1989 through 1999 at 0.68 ± 0.07%. During 2000, the incidence of *C. difficile* colitis increased significantly to 1.2% (343/29,626; $P < .0001$); accordingly, from 1999 to 2000, the number of positive cytotoxin assays increased from an average of 6 per month to 18 per month. In addition, 314 of these 2,334

Table 2. *CLOSTRIDIUM DIFFICILE* COLITIS (CDC) AS A SIGNIFICANT OVERALL CAUSE OF DEATH

	1989–2000		1999		2000	
	Number	%	Number	%	Number	%
Hospital admissions	345,600		27,743		29,626	
Number of patients with CDC	2,334		206		343	
Autopsy-diagnosed deaths*	12/2,334	0.51	0/206	0	2/343	0.58
Colectomies for CDC*	26/2,334	1.1	1/206	0.48	9/343	2.6
Deaths after colectomy	25/44	57.0	2/2	100	11/16	69.0
Incidence fulminant symptoms*	38/2,334	1.6	1/206	0.48	11/343	3.2
Overall deaths from CDC*	27/2,334	1.2	1/206	0.48	7/343	2.0
Incidence of CDC	2,334/345,600	0.68	206/27,743	0.74	343/29,626	1.2
Overall hospital death rate			957/27,700	3.5	996/29,626	3.4
Hospital death rate from CDC			2/957	0.21	14/996	1.4

* Excludes all patients transferred with fulminant symptoms.

patients died during their hospital stay with at least one positive stool *C. difficile* toxin assay. The all-causes death rate for any patients with the diagnosis of *C. difficile* colitis was 13.5% (314/2,334), greater than the overall hospital death rate of 3.4%. The average age of these patients was 62.4 ± 16.8 years and the average length of hospital stay was 23.9 ± 29.4 days.

Figure 1 shows the number of patients diagnosed with *C. difficile* colitis per month. The overall incidence of disease-specific death or colectomy in patients with *C. difficile* colitis was 1.6%, ranging from 0% in 1990 to 3.2% in 2000. This was calculated excluding patients transferred into our institution with the primary diagnosis of fulminant *C. difficile* colitis (27 overall patients, 1 in 1999 and 9 in 2000). Figure 2 shows the colectomies and autopsy rate per year since 1989.

Patient Characteristics

The mean age of patients undergoing colectomy was 65 ± 13 years (Table 3). Age significantly predicted survival (69 vs. 60 years, P = .015 by Mann-Whitney rank sum). No patient younger than 50 died, and none older than 80 survived colectomy. There was no difference in the death rate between the

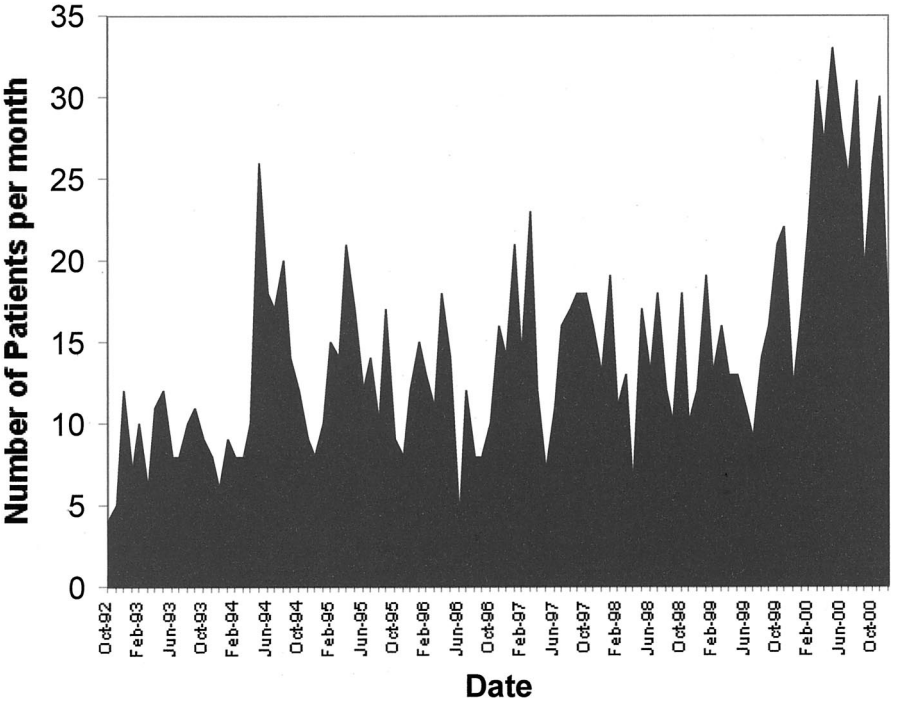

Figure 1. The monthly incidence of *Clostridium difficile* colitis has increased from the years 1999 to 2000.

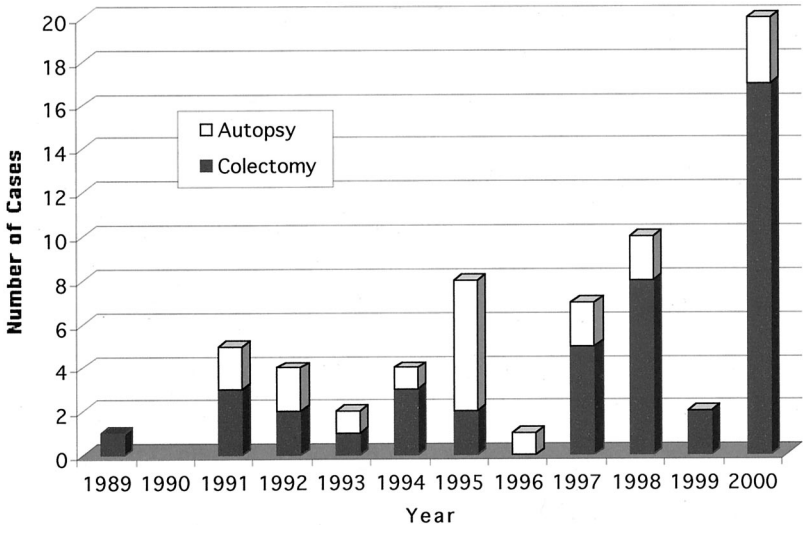

Figure 2. Number of patients with morphologic proof of *Clostridium difficile* colitis requiring colectomy or dying.

sexes, although significantly more men then women had fulminant *C. difficile* colitis (58% vs. 42%).

Table 4 lists specific characteristics of patients with fulminant colitis. Seventy-five percent of patients undergoing colectomy had recently (within 2 months) undergone surgery. The indication for the 38 operations is listed in Table 4. Cardiothoracic procedures were the most common operation that preceded fulminant colitis, followed by vascular surgery and transplantation.

Of the 64 patients with fulminant colitis, 22% of patients had a previously documented and successfully treated history of *C. difficile* colitis. Admitting symptoms were referable to *C. difficile* colitis in 34% of patients; in the remaining 65%, *C. difficile* colitis developed while the patient was an inpatient for other reasons (23% medical admissions, 42% surgical admissions) (Table 5). Excluding patients admitted with symptoms of *C. difficile* colitis, 81% (22/27) of patients on surgical services in whom fulminant colitis developed underwent colectomy, compared with only 33% (5/15) of those on medical services ($P = .011$, Mann-Whitney rank sum). Of patients diagnosed at autopsy, 35% (7/20) did not have a correct premorbid diagnosis, whereas only 11% (5/44) of the colectomy patients were undiagnosed before surgery. In 11% (5/44) of patients undergoing colectomy, anticlostridial treatment was never started because they presented to surgical services with peritonitis, hypotension, or both. Twenty percent of all patients did not have diarrhea and presented with abdominal distention and ileus.

Table 3. AGE AND SEX OF PATIENTS WITH FULMINANT *CLOSTRIDIUM DIFFICILE* COLITIS

	Mean Age	Male	Female
Colectomy—all*	65 ± 3	28/44 (64%)	16/44 (36%)
Colectomy—survived	60 ± 15*	12/19 (63%)	9/21 (43%)
Colectomy—died	68 ± 10*	16/25 (64%)	9/25 (36%)
Autopsy	60 ± 16	9/20 (45%)	11/20 (55%)
All*	64 ± 13	37/64 (58%†)	27/64 (42%*)

*† $P < .05$.

Transplant patients were more likely to undergo colectomy and more likely to survive after the development of fulminant colitis. Table 4 shows that 32% (14/44) of patients who underwent colectomy were immunosuppressed, as were 65% (13/20) of patients in the autopsy group. Of those undergoing colectomy, patients with a previous organ transplant (n = 12) had a better survival rate compared with nontransplant patients (n = 32) (58% vs. 37%; $P < .05$). Of the entire cohort, 23% (15/64) patients had undergone a previous organ transplant, whereas 19% (12/64) were immunosuppressed by other conditions. Of this latter group, only 2 of these 12 underwent colectomy (1 died), whereas the remaining 10 were in the autopsy group. Three of 15 transplant patients died without undergoing colectomy for fulminant *C. difficile* colitis.

Table 5 lists the incidence of *C. difficile* colitis in patients who had undergone lung transplantation. Thirty-one percent of patients who had received lung transplants (78/250) had a documented history of *C. difficile* colitis, and in 13% (10/78) fulminant colitis developed (eight colectomies, two autopsies), with an overall death rate of 50%. These patients were more likely to have fulminant symptoms compared with all patients with *C. difficile* colitis (13% vs. 1.6%, $P < .001$), but the death rate was not higher.

Table 4. CHARACTERISTICS OF 64 PATIENTS WITH FULMINANT *CLOSTRIDIUM DIFFICILE* COLITIS (CDC)

	Colectomy		Autopsy		Total	
	Number	%	Number	%	Number	%
Immunosuppressed	14	32*	13	65*	27	42
Transplant	12	27*	3	15*	15	23
Lung	8	18	2	10	10	16
Heart	2	5	0	0	2	3
Liver	2	5	0	0	2	3
Kidney	0	0	1	5	1	2
HIV	0	0	2	10	2	3
Heme disease	0	0	3	15	3	5
Autoimmune	2	5	2	10	4	6
Chemotherapy	0	0	2	10	2	3
Recent Postop	33	75*	5	25*	38	59
Neurosurgery	1	2	0	0	1	2
Head and neck	1	2	0	0	1	2
Gynecology	2	5	1	5	3	5
Transplant surgery	5	11	1	5	6	9
Trauma	3	7	0	0	3	5
Vascular surgery	5	11	2	10	7	11
General surgery	2	5	0	0	2	3
Urologic surgery	0	0	1	5	1	2
Orthopedic surgery	0	0	1	5	1	2
Thoracic nontransplant	3	7	0	0	3	5
Heart valve	3	7	0	0	3	5
Valve and CABG	2	5	0	0	3	5
Coronary bypass	6	14	0	0	6	9
All cardiothoracic	19	43	1	5	18	28
Previous CDC history	11	25	3	15	14	22
Transfers	19	43	8	40	27	42

CABG, coronary artery bypass grafting.
* $P < .05$.

Symptom Progression

The rapidity of disease progression is described in Table 6. None of these variables significantly predicted survival. The median length from admission to colectomy in those who were admitted with a diagnosis of *C. difficile* colitis was 2 days. Thirty-six percent of patients (16/44) underwent colectomy within 7 days of the onset of symptoms (Fig. 3).

Laboratory Findings and APACHE Scoring

The average white blood cell count for the entire group of patients with fulminant colitis was 36,100 ± 30,000 (range 600–172,000). The average fraction of unsegmented (band form) neutrophils for the entire group was 30 ± 13% (range 10–62). Only five patients had white cell counts in the normal range (2000–12,000), and all of these had band form percentages greater than 20%. There was no significant difference in white cell or band percentage in survivors compared with nonsurvivors. In survivors and nonsurvivors, lactate levels before colectomy were 1.6 ± 2.2 and 3.0 ± 2.23, respectively

Table 5. SURVIVAL AFTER COLECTOMY FOR *CLOSTRIDIUM DIFFICILE* IN TRANSPLANT PATIENTS VERSUS NONTRANSPLANTED PATIENTS

	n	Percentage Survived
Transplant	12	58*
Nontransplant	32	37*
Immunosuppressed, nontransplant	2	50
Epidemiology of *Clostridium difficile* in lung transplant population		
	n	Percentage
Number of lung transplants 1990–2000	250	
Number who developed *C. difficile* colitis	78/250	31
Number who died at autopsy without colectomy	2	1
Number who required colectomy	8	3
Percent of patients with colitis who develop fulminant symptoms	10/78	13

* $P < .05$.

Table 6. RAPIDITY OF PROGRESSION

	Median Time (days)	
	Survivors	Nonsurvivors
Admission to surgery	12	16
Symptoms to surgery	15	7.5
Confirmed diagnosis to surgery	5	5
Positive toxin to surgery	9	3
Computed tomography scan to surgery	2	1
Surgery until death		8
Admission to death (autopsy group only)		9.5

Table 7. FALSE-NEGATIVE RATE OF DIAGNOSTIC STUDIES FOR FULMINANT *CLOSTRIDIUM DIFFICILE* COLITIS

	Colectomy	Autopsy	False-Negative Rate
Endoscopy	1/18	1/2	10%
Computed tomography scan	0/30	0/9	0%
Fecal leukocytes	6/10	0/0	60%
Toxin assay	3/33	3/15	12.5%

(not significant). Base deficit (−7.3 vs. −7.7) and arterial pH (7.37 vs. 7.30) also did not appreciably distinguish survivors from nonsurvivors after colectomy.

APACHE III data were available for 20 patients with fulminant colitis. The median APACHE III score in these patients was 114. Nonsurvivors (n = 15) had a median score of 117 versus 88 for survivors. The difference was not statistically significant ($P = .15$). APACHE III scores increased daily before colectomy was performed (each day significantly different, $P < .01$) (Fig. 4). The maximum precolectomy predicted hospital death rate of nonsurvivors and survivors was 83 ± 13% versus 56 ± 28% (not significant), and the average predicted hospital death rate was 73 ± 24%.

Diagnostic Studies

A computed tomography (CT) scan was performed in 39 patients and, when combined with the clinical scenario, was diagnostic in all. All scans showed ascites (mild to massive) and colonic wall thickening or massive colonic dilation (Fig. 5). Findings showed predominantly right-sided colitis in 11 patients, left-sided colitis in 9 patients, and pancolitis in 19 patients. Neither intravenous nor oral contrast was necessary for diagnostic accuracy. Endoscopy was performed in 20 patients (8 flexible sigmoidoscopies, 12 colonoscopies). Flexible sigmoidoscopy did not demonstrate pseudomembranes in two patients. Disease restricted to the right side was subsequently found on surgical pathology in one, and the other had a poor prep. The false-negative rate for endoscopy was 10% (2/20), although all colonoscopies that reached the right colon were positive. Frank perforation was rare. A small amount of retroperitoneal gas was seen in one patient on a CT scan; this patient died immediately after the scan. Another patient at autopsy had free air from a colon perforation. This patient did not have a CT scan performed.

By contrast with CT, the cytotoxin assay had a false-negative rate of 12.5% (6/48) (Table 7). Patients who died without colectomy were significantly more likely to have had a false-negative toxin assay (20% vs. 9.1% false-negative rate, $P < .05$). Fecal leukocytes were examined in only

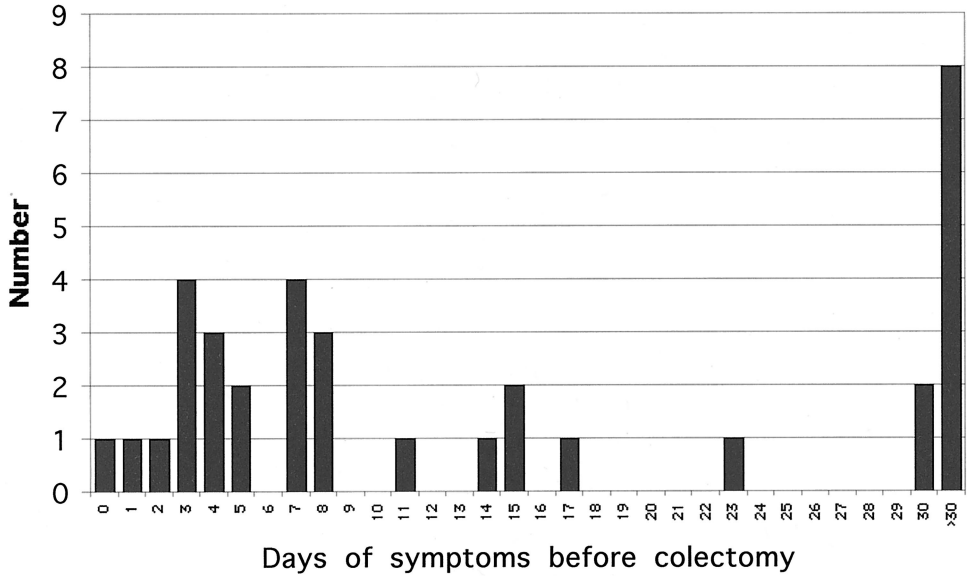

Figure 3. Time interval from initial symptoms to colectomy or death in patients with fulminant *Clostridium difficile* (median 9 days).

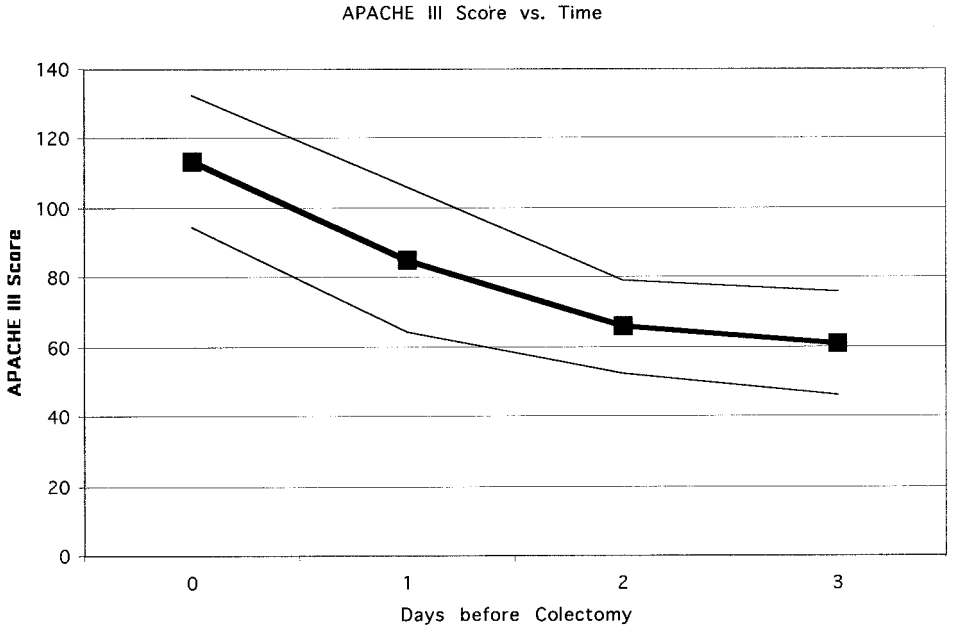

Figure 4. APACHE III scores (thin lines are one standard deviation) as a function of days before colectomy in 20 patients with fulminant *Clostridium difficile*.

10 patients; 6 were negative. In patients undergoing colectomy, CT scan, endoscopy, and toxin assay was the first study to confirm the diagnosis of *C. difficile* colitis in 37%, 13%, and 50%, respectively. Patients diagnosed first by CT scan were more likely to survive colectomy than those diagnosed initially by endoscopy or toxin (71%* vs. 25% vs. 25%*, respectively; $*P < .05$). Of the six patients with negative toxin assays, four had CT scans. One showed right-sided colitis; the other three showed pancolitis. Two patients with a negative toxin assay had positive findings on flexible sigmoidoscopy.

Surgical Treatment and Results

Thirty-nine patients (89%) underwent a total abdominal colectomy and end ileostomy. A right hemicolectomy with ileostomy was performed in four patients with disease limited strictly to the right side (seen on intraoperative colonoscopy); all survived. One ileostomy without colectomy was performed in a patient who subsequently died. Seven nontherapeutic laparotomies were performed; six of them resulted in death (four patients were diagnosed only at autopsy). Three patients eventually had a colectomy, but only one survived. Four patients returned to the operating room emergently with hemoperitoneum, three from the retroperitoneum and one from the liver. Three underwent splenectomy (two for bleeding, one for infarction). The requirement for preoperative vasopressors (n = 37) significantly predicted death after colectomy (65% vs. 14%; $P = .036$, Mann-Whitney rank sum). The overall death rate after colectomy was 57%.

DISCUSSION

In most patients, *C. difficile* colitis resolves after treatment with metronidazole or vancomycin; however, in a significant minority progressive systemic symptoms develop despite appropriate and timely medical therapy. The most striking finding of this study is the significant and increasing number of deaths from a disease considered indolent and responsive to treatment. Indirectly, we infer that timely intervention, both medical and surgical, may improve outcome. This is supported by the lower death rate for surgical intervention before the institution of vasopressors.

The reported incidence of fulminant *C. difficile* colitis ranged from a low of 0% in 1990 to 3.2% in 2000. An accurate incidence of fulminant *C. difficile* colitis is, however, difficult to estimate. It is likely that we grossly underestimated the death rate of *C. difficile* colitis. This study certainly did not capture all patients who died of fulminant *C. difficile* colitis because only patients with gross, histologic, and clinical confirmation of the diagnosis were included. A number of patients who had the clinical diagnosis of fulminant colitis on the death summary were not included because pathologic confirmation was not obtained. The fact that 35% of our patients were first diagnosed only at autopsy strongly suggests that a significant number of intensive care unit deaths attributable to "sepsis" may have been secondary to fulminant *C. difficile* colitis. The death rate for patients with *C. difficile* colitis was 13% compared with the overall hospital death rate of 3%, suggesting that *C. difficile* colitis is either a marker for a critically ill patient population or a significant contributor (either directly or indirectly) to death.

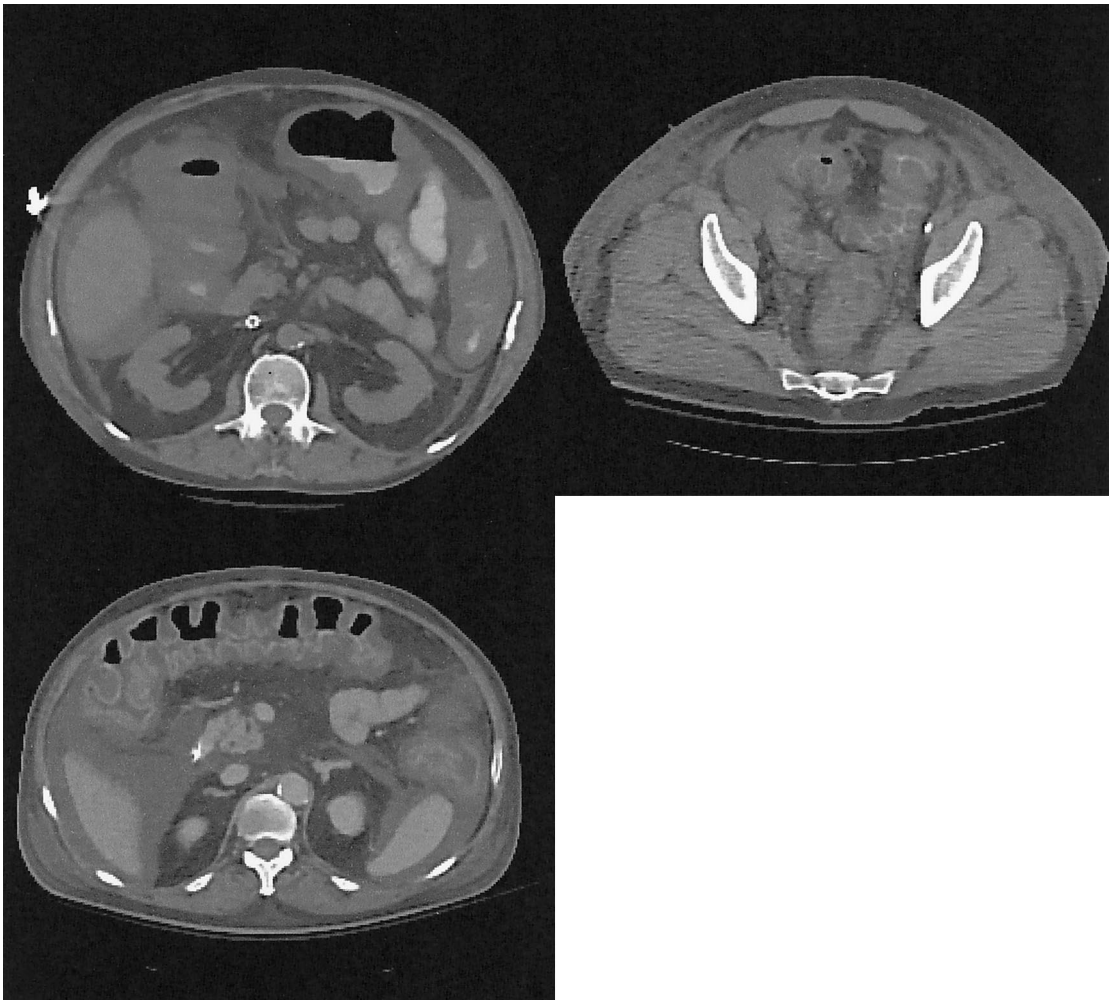

Figure 5. Abdominal computed tomography scans from three patients with findings diagnostic of fulminant *Clostridium difficile* colitis. Patients with systemic symptoms from *C. difficile* colitis in whom thickening and dilatation of the colon and ascites develop require a colectomy.

The reason for the increased incidence is not clear. We believe that this is not due to a decreased threshold for colectomy or an improved recognition of disease. In addition, because 40% of patients were transferred from various hospitals throughout western Pennsylvania with the diagnosis of fulminant *C. difficile* colitis, we do not believe that the disease is isolated to our medical center. Our preliminary data suggest that organisms isolated from patients with fulminant *C. difficile* colitis are neither of any specific subtype nor are resistant to metronidazole.

The fulminant manifestation of the disease has been poorly characterized in the literature. The clinical syndrome of fulminant *C. difficile* colitis can be recognized with a proper knowledge of the spectrum of disease presentation. Although diarrhea is the hallmark of *C. difficile* colitis, fulminant colitis may be difficult to diagnose because diarrhea may be absent secondary to severe colonic dysmotility. Even when present, diarrhea may be perceived to be a minor component of a nonspecific septic picture. We consider the fulminant version of *C. difficile* colitis to be present when a patient exhibits systemic signs of toxicity (fever, hypotension, tachycardia, leukocytosis, and/or volume requirements). Hypotension is a late finding and can be resistant to vasopressor support. Abdominal signs range from distention to generalized tenderness with guarding. Impressive leukemoid reactions are frequent and occur early. Death generally occurs before free air and perforation develop. Contrary to the literature, perforation is only rarely part of the clinical syndrome (2/64 patients). The syndrome often appears in hospitalized patients with confounding acute medical issues that may contribute to delays in diagnosis. Once hypotension develops, we consider the patient at a high risk for death unless the systemic disease can be controlled, usually with colectomy.

An important hint of impending fulminant *C. difficile* is the rapid elevation of peripheral white blood cell count to extraordinary levels (30-50,000) accompanied by a significant bandemia and sometimes a significant increase in progenitor cells (myelocytes, metamyelocytes, nucleated red blood cells, promyelocytes). This almost always preceded

hemodynamic instability and the development of organ dysfunction. The time between onset of symptoms and hemodynamic instability may vary from hours to weeks. Even in patients who have had relatively benign symptoms for weeks, unexpectedly rapid progression to shock may occur. Predicting those who will fail to respond to medical therapy has been very difficult, so that early warning signals such as a progressive leukemoid reaction may be invaluable. Identification of groups at especially high risk may decrease the threshold to institute treatment.

Several patient characteristics stand out as risk factors for the development of fulminant *C. difficile* colitis. Immunosuppression was a common characteristic for the entire patient cohort (28/64). Twenty-seven percent of patients who underwent a colectomy had had a solid organ transplant, but they paradoxically had improved outcome, probably because of improved awareness, lower thresholds for surgery, and closer follow-up. Immunosuppressed, nontransplant patients represented 50% of the patients who underwent autopsy and 5% of patients undergoing colectomy. Immunosuppression seems to be a significant risk factor for the development of fulminant *C. difficile* colitis. Increased use of antibiotics, a concomitant suppression of antiinflammatory cytokines, and inability to mount an antibody-mediated response to toxins may all play some role.[11,17] The lung transplant population appears especially susceptible to *C. difficile* colitis. This group was more likely to have fulminant symptoms than other patient groups–including other transplants. In fact, in 31% of all lung transplant recipients, *C. difficile* colitis developed (total hospital incidence 0.68%). Lung transplant recipients tend to require more immunosuppression to protect against frequent episodes of rejection. In addition, frequent pulmonary infections require repeated courses of antibiotics. A true incidence can be calculated in this group because all such patients received their transplants in our hospital, and hospital follow-up was 100%. These patients were more prone to have fulminant symptoms compared with all patients with *C. difficile* colitis (13% vs. 1.6%, $P < .001$), but the death rate after colectomy was not higher.

A prior diagnosis of successfully treated *C. difficile* colitis was common among patients with *C. difficile* colitis. Some of these patients were admitted with advanced recurrent disease. Other patients suffered exacerbations when readmitted for unrelated disease. Seventy-five percent (33/44) of patients who required a colectomy for fulminant *C. difficile* colitis had a recent surgical procedure or were on surgical services. Of these 33 patients, 19 (54%) had heart or lung surgery. Thus, patients with a previous history of *C. difficile* colitis who undergo a major operation unrelated to the gastrointestinal tract appear to be at high risk for fulminant disease.

Although no assay system is perfect for the diagnosis of *C. difficile* colitis, the most reliable method is the standard cytotoxin assay to identify the presence of toxin A in stool.[18] Unfortunately, the assay takes up to 48 hours. In this study, the median time between the onset of symptoms and the return of a positive toxin result was 6 days. There is often considerable delay in recognizing the symptoms and in obtaining a stool sample. Patients who died of fulminant *C. difficile* colitis without colectomy were twice as likely to have had a false-negative toxin (diagnosis confirmed by autopsy). The institution of treatment on a presumptive basis before more definitive cytotoxin results return may eliminate treatment delay and, thus, some of the complications. Improvement on medical therapy for *C. difficile* colitis should occur rapidly; resolution of symptoms takes an average of 3 to 5 days.[19] Patients who do not respond within this period should be closely monitored for systemic symptoms and the development of a toxic megacolon.

In patients with the fulminant syndrome, CT scan and endoscopy can quickly diagnose *C. difficile* colitis. In patients without other clear-cut indications for laparotomy, these studies can be performed quickly when the diagnosis of fulminant *C. difficile* colitis is entertained. CT scan proved to be a useful tool in the diagnosis of *C. difficile* colitis even without the use of potentially nephrotoxic intravenous contrast agents. Every patient who underwent a CT scan had evidence of ascites, colon wall thickening, and/or dilation. These CT scan findings may prove helpful in categorizing the severity of the colitis when interpreted in light of the clinical history.

Although preoperative diagnosis is helpful in surgical planning, *C. difficile* colitis can be diagnosed during surgery, even though the external appearance of the colon may be nonspecific with an edematous, boggy colonic wall, pericolic inflammation, and serous sterile ascites. The surgical findings may not intuitively suggest the appropriate treatment. In fact, seven patients in the current series underwent a "nontherapeutic" laparotomy, and all died or required subsequent colectomy. Intraoperative colonoscopy can secure the diagnosis when there is doubt. The procedure of choice is a total abdominal colectomy and end ileostomy. Although all four patients who had a right hemicolectomy survived, these were a select group who had no evidence of left-sided colitis on intraoperative colonoscopy. Limited resections should be done cautiously.

The results of colectomy for fulminant disease are often disappointing. The overall death rate was 57% after colectomy. Death rates after colectomy in small series range from 38% to 80%.[13,20] The most striking factor associated with death after colectomy is the need for preoperative vasopressors. We previously reported that an indication for colectomy in patients with *C. difficile* colitis is a need for vasopressors;[12] however, our more recent findings suggest that once this occurs, the perioperative death rate more than quadruples compared with patients who undergo colectomy before vasopressors are required. This study should emphasize the importance of preventative measures through infection control and early recognition and treatment of patients with symptoms of *C. difficile* colitis.

In summary, fulminant *C. difficile* colitis is an underap-

preciated cause of death secondary to its nonspecific clinical syndrome and lack of general awareness of the spectrum of clinical disease. Patients with immunosuppression or a prior history of successfully treated *C. difficile* colitis and those who have undergone recent surgical procedures seem at highest risk. Fulminant *C. difficile* colitis has a very high death rate once the requirement for vasopressors has been initiated. Rapid diagnosis and treatment are crucial to a positive outcome, and early surgical intervention should be used in medically unresponsive patients. Surgical intervention for fulminant *C. difficile* colitis is certainly far from ideal and carries a very high complication rate. Future work is needed in the development of improved medical treatments, such as specific antitoxin hyperimmune globulin and inhibitors of the proinflammatory cascade.[8,21,22]

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